ANNALS OF SURGERY
Vol. 220, No. 4, 520–535

Regional Chemotherapy for Melanoma

A 35-Year Experience

Edward T. Krementz, M.D., R. Davilene Carter, M.D., Carl M. Sutherland, M.D., James H. Muchmore, M.D., Robert F. Ryan, M.D., and Oscar Creech, Jr., M.D.*

From the Tulane University School of Medicine, Department of Surgery, and the Tulane Cancer Center, New Orleans, Louisiana

Objective

The authors present their 35-year experience with intra-arterial chemotherapeutic regional perfusion of 1139 patients with melanomas, using an extracorporeal oxygenated circuit and heart-lung apparatus.

Summary Background Data

Intra-arterial chemotherapy produces improved responses in many tumors. By isolating and sustaining the area with extracorporeal oxygenated circulation, high doses can be delivered to the tumor area, limited only by local toxicity. Drug levels up to 10 times those achieved by systemic administration are obtained.

Methods

Techniques for hyperthermic perfusion were developed for limbs, pelvis, head, neck, and skin of the breast. Melphalan (Burroughs Wellcome, Research Triangle Park, NC) was used in 753 patients. Combinations with melphalan or other drugs were used in remaining cases at temperature of 38 to 40 C for 30 to 60 minutes.

Results

Chemotherapy perfusion followed by tumor excision or node dissection, was performed where indicated. The cumulative 10-year survival for patients with localized melanomas was 70%. For patients with local recurrences or satellites within 3 cm, survival was 61%. For those with regionally confined intransit tumors, survival was 30%; for those with regional node involvement, 38%; for those with intransit and nodal metastases, 16%; for those with distant metastases and perfusion—mainly to save functional limbs—survival was 7%. Multiple perfusions were performed in 158 patients with recurrent disease on 366 occasions. Patients with indolent regionally confined melanomas were benefited by prolongation of useful life.

Conclusions

Safe perfusion techniques are available for most anatomic regions. Increased chemotherapeutic doses are delivered to isolated areas limited only by local toxicity. Adjunct perfusion in poor prognosis stage I cases is useful in reducing local recurrence, and intransit or lymph node metastases. Regional perfusion reduces the need for major amputation. Multiple perfusion can be useful in treating recurrent chronic melanoma.

In 1956, experimental studies were begun in the laboratories of the Department of Surgery at Tulane University School of Medicine (Tulane) to increase the chemotherapy dosage in isolated tumor-bearing regions of the body supported by an extracorporeal oxygenated circulation maintained by a heart-lung machine. Further isolation was obtained by an appropriately placed tourniquet. Increased dosage delivered through the pump circuit was achieved, limited only by local toxicity to blood vessels, nerves, and other tissue in the treated areas. By 1957, chemotherapeutic perfusions of the hind limb, midgut, and liver had been developed in the experimental animal.[1] Serious local ill effects could be avoided by using low-flow rates and pressures below the mean systemic arterial blood pressure. Perfusions lasting longer than 90 minutes were associated with increased edema and ischemia in the perfused tissues.

In June 1957, a 76-year-old patient at Charity Hospital of Louisiana at New Orleans (CHNO), who had been treated for melanoma of the right ankle 2 years before by wide excision and a superficial groin dissection, was admitted with more than 80 satellites confined to the skin of the lower limb. The patient refused amputation, which was the treatment generally recommended then. Instead, a chemotherapeutic perfusion of the limb was performed through the common femoral vessels with melphalan (Burroughs Wellcome, Research Triangle Park, NC), a drug undergoing evaluation by oral administration for treatment of metastatic melanoma. Despite the poor solubility of melphalan in aqueous solution, the patient experienced a slow but complete tumor response with minimal systemic toxicity. At that time, responses in melanoma to systemic chemotherapy were partial and occurred in less than 10% of patients.[2] The patient remained melanoma-free and died 16 years later at age 92. This response was gratifying, stimulated trials in a variety of tumors with the few agents available, and resulted in the development of techniques designed to perfuse various anatomic regions or single organs.

Funded in part by the Armande Billion Cancer Research Fund, the Ladies Auxiliary of the Veterans of Foreign Wars of the United States, the Catherine and Hunter Pierson Cancer Research Fund, and the American Cancer Society, Grant CA 18007, from the National Cancer Institute DHEW.

Send reprint requests to Edward T. Krementz, M.D., Professor of Surgery, Emeritus, Tulane University School of Medicine, Department of Surgery, 1430 Tulane Avenue, New Orleans, LA 70112.

*Deceased.

Accepted for publication April 11, 1994.

Melphalan used in this study was provided by Burroughs Wellcome Company, Research Triangle Park, North Carolina.

Triethylene thiophosphoramide used in this study was provided by Lederle Laboratories, American Cyanimid Company, Pearl River, New York.

In 1958, Creech presented the results to the American Surgical Association; this included 24 patients with advanced cancer treated during the previous 10 months.[3] Eighteen of the 19 patients treated long enough for changes to become apparent had demonstrable, remarkable tumor necroses, often occurring in neoplasms that were not thought to respond to mustard compounds.

In 1962, we reported our Phase II studies to the American Surgical Association with the early results of 303 patients—123 with melanomas, 105 with carcinomas, 48 with sarcomas, and 27 with glioblastomas—in whom a complete or partial response rate of 68% was achieved.[4] The best and longest responses occurred with melanomas and sarcomas of the limbs, and we present our 35-year experience with regional perfusion for 1139 patients with melanomas.

MATERIAL AND METHODS

Advantages

Increased chemotherapeutic dosage in the regional areas under therapy avoids severe systemic toxicity. Drug levels of six to ten times more than those obtained by systemic administration are achieved. Intra-arterial administration of drug provides a complete saturation of the tumor. Isolation by catheterization of the major artery and vein supplying the area and the additional compression of collateral circulation by the tourniquet minimize the drug loss. This reduces systemic toxicity and protects the immune defenses of the host. Local toxicity limits the obtainable drug levels, but appropriate safe dosages have been determined. Washout of the toxic end-products and residual active drug on completion of the perfusion further decreases systemic toxicity and local complications.

Additional advantages have been achieved. The bubble oxygenator for extracorporeal perfusion causes an increased partial pressure of oxygen (pO_2) level of approximately 400 mm Hg, which potentiates the effect of alkylating agents and has its own tumoricidal effects.[5] In effect, a temporary hyperbaric chamber is created in the perfused area that benefits patients undergoing irradiation. Hyperthermia from perfusate temperatures of 40 C to 41 C and external applied heat produce additional tumoricidal effects.[6,7] Hyperthermia increases the action of chemotherapeutic agents, increases the metabolic activity, and vasodilation of the tumor vasculature. Heparinization required for extracorporeal circulation has antimetastatic effects by inhibiting the adherence of tumor cells to vessel walls and has its own selective tumoricidal action.[8]

Indications

The indications for melanoma perfusion for limbs or other sites for patients who can tolerate a 3- to 4-hour operation and have no or minimal peripheral vascular disease are 1) for definitive treatment of intransit metastases, nonresectable recurrent or primary tumors; 2) as an adjunct to surgical excision for regionally confined, poor-prognosis melanoma; 3) to convert advanced nonresectable lesions to operability; and 4) palliation in noncurable recurrent cancer by maintaining a functional limb in the presence of systemic metastases or a result of metastases to a limb from centrally located melanomas.

For adjunctive treatment coupled with wide excision in stage I melanoma of the limb, perfusion is appropriate for tumors that can be included in the isolated area and are Clark Levels III to V in depth (1.5 mm or thicker). Before 1969 and 1970, when Clark's levels and Breslow's thickness classifications were introduced, melanomas pathologically classified as "invasive" were included.

Currently, indications for adjunctive perfusion include other serious prognostic indicators, such as nodular or acral lentiginous melanomas; long-standing, large, or anaplastic lesions; and melanomas involving the feet and hands, particularly the plantar or palmar surfaces or subungual sites.

Techniques

Techniques for regional perfusion of the limbs have been described in detail in current publications (Fig. 1).[9,10] Techniques for perfusion of the head and neck—originally reported by Aust and colleagues,[11] the forequarter, the pelvis, the hindquarter, and the liver and other organs also are described. The technique we developed for liver perfusion in the experimental animal was not used in our early clinical studies. Ausman and Aust reported on liver perfusion in 1960[12]; they were followed by Mulcare and colleagues in 1973.[13] Aigner and colleagues, in 1983, simplified and expanded the use of liver perfusion.[14]

With the introduction of hyperthermia for perfusion, temperatures were raised to 40 C to 41 C[7]; however, because of increased toxicity, heated perfusions with limb temperatures of 38 C to 40 C currently are used more frequently. Elevated limb temperatures are obtained more readily by raising operating room temperatures to 21 C (71 F) during prepping and draping, using a warming mattress kept at 40 C. Limb temperatures are monitored by four or more subcutaneous thermistor probes. We currently use a Bentley Bio-2 infant heart-lung bypass oxygenator (Bentley Laboratories, Irvine, CA) and Sarns Modular Cardiac Bypass Pump with controls for temperature and flow (Sarns, Ann Arbor, MI). This equipment must be operated by a certified cardiopulmonary perfusionist with experience in limb or organ perfusion.

For upper-limb melanomas, perfusion is performed through the first portion of the axillary artery and vein. For lower-limb melanoma, the external iliac vessels are used for the groin or upper thigh lesions, and common femoral vessels are used for lesions at mid thigh or lower. Head and neck perfusions are performed through the external carotid artery and common facial vein. Forequarter perfusions are performed by cannulating the subclavian vessels directly or by using retrograde catheter placement. Pelvic perfusions are carried out by direct and retrograde techniques through the distal aorta and lower vena cava. Hindquarter perfusions are performed through the common iliac vessels. Brain perfusions originally were developed by Woodhall and colleagues,[15] but the development of chemofiltration techniques, originally reported by Dedrick and colleagues for brain perfusion[16] and more fully developed by Aigner for liver or pancreas perfusions,[17] allow the returning venous blood to pass through a filtering or dialysis device to remove excess or unbound chemotherapeutic agents and have facilitated perfusion of these organs or the pelvis or hind or forequarter, where regional isolation is incomplete. For limb perfusion, proximal larger vessels are easier to cannulate and repair and permit higher flows, rapid warming, and increased tissue oxygenation, but do not achieve as good isolation as more distal perfusions.

Drugs and Dosages

Melphalan (Alkeran), commonly known as phenylalanine mustard or I-PAM, was selected for the first melanoma perfusion; it was reported by Luck that phenylalanine, a metabolite of melanin, would carry attached alkylating radicals into the melanoma cell and showed promise in a mouse melanoma system.[18] It is a long-acting, mildly vesicant alkylating agent, poorly soluble in water, but readily soluble in alcohol or propylene glycol. The intravenous form of melphalan (soluble acid salt) was only released in the United States in 1993, for treatment of multiple myeloma; therefore, its use by perfusion must be approved by each hospital's institutional review board.

Triethylene thiophosphoramide (Thiotepa or TSPA [Lederle Laboratories, Wayne, NJ]) also is used because it has similar properties to melphalan. When melphalan was not available, TSPA was used at the same dosage.

Nitrogen mustard (HN_2) is an effective, rapidly acting alkylating agent, but is a severe vesicant and increases the risk of local toxicity. It particularly is dangerous to peripheral nerves, and neuritis or paralysis may result with its use. Melphalan and TSPA are given in doses of

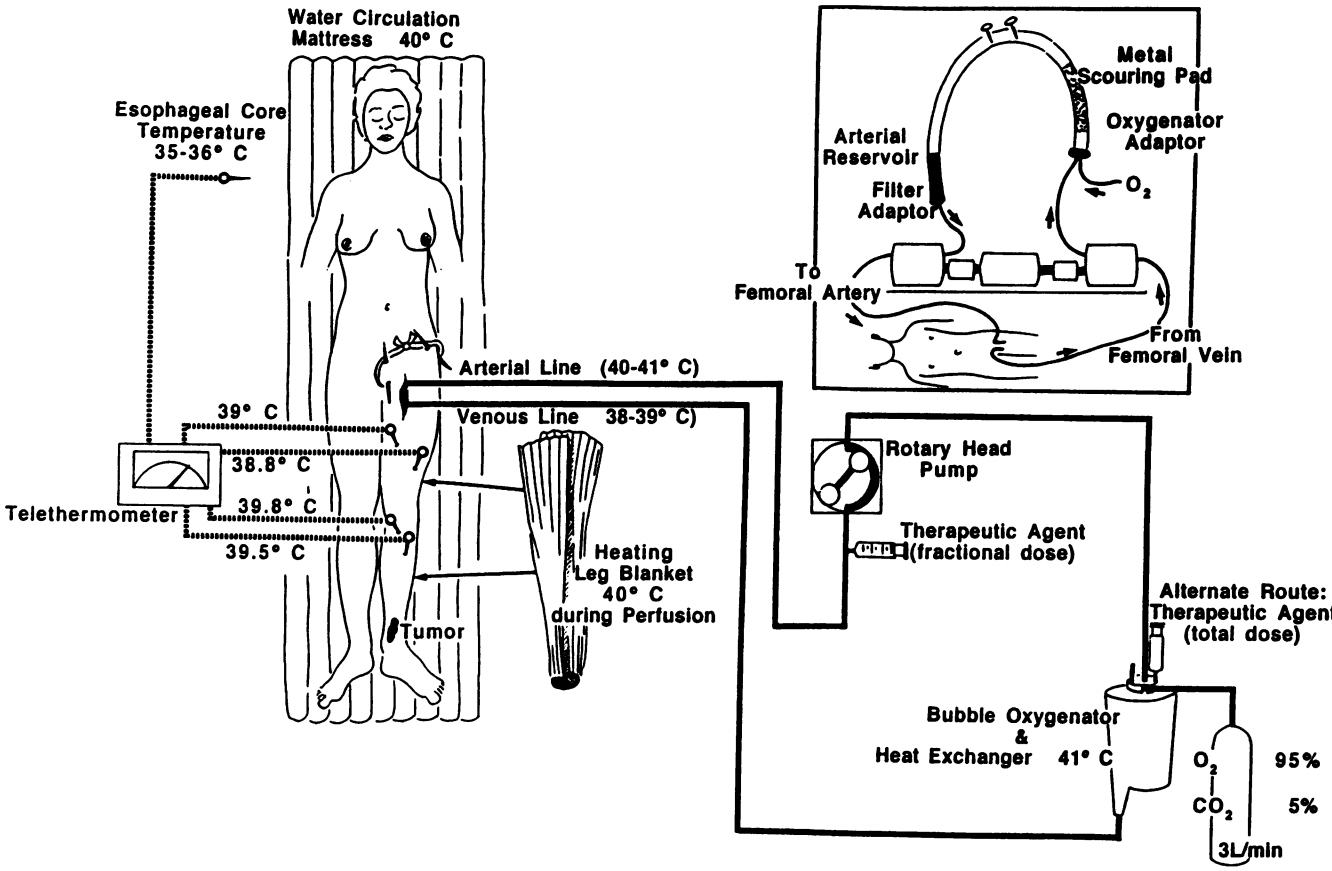


Figure 1. Flow diagram of perfusion 1957 compared with 1992.

10- to 20-mg aliquots into the arterial line at 3-minute intervals, or as a single dose in the pump reservoir. Opinion still is divided as to which method is safest and most effective. Nitrogen mustard is given in 1- to 2-mg aliquots in the arterial line at 1- to 3-minute intervals until the total dose is given. The perfusion is discontinued 10 to 20 minutes after the last dose because the drug is hydrolyzed rapidly. Dosages as used at Tulane are listed in Table 1, and Table 2 lists dosages reported by other investigators.

Dosage Determination

Originally, melphalan was used in doses of mg/kg of ideal or actual body weight, whichever was the lesser. Accommodation was made for proportional size of limbs compared with the rest of the body, and dosage was modified downward in fair-skinned or elderly patients, or patients who were chronically ill. Young patients with well-developed muscles can tolerate increased doses.

Wieberdink and colleagues in Holland recommended the melphalan dosage be calculated on the basis of limb volume, as determined by water displacement.[22] They recommended 10 mg/L of limb volume for either upper or lower limbs. Our studies showed that upper limbs would tolerate 13 mg/L of limb volume, whereas 10 mg/L of limb volume was satisfactory for lower limbs.[23] Larger doses can be used safely if whole blood is used for the perfusate and the volume is increased.[24]

These recommendations were incorporated into the adjunctive perfusion protocol adopted by the cooperative adjunctive study for stage I melanoma, sponsored by the International Melanoma Study Group, the European Organization for Research and Treatment of Cancer (EORTC), and the North American Perfusion Group through the cooperation of the Southwest Oncology Group (SWOG) in 1984.

Lejeune and colleagues and the International Melanoma Study Group give the entire dose into the pump reservoir in one aliquot once the appropriate temperature has been reached. They recommend reducing the reservoir temperature to 38 C during the administration of the drug to the reservoir and keeping the temperature reduced for 10 minutes.

Boddie and colleagues recently completed a cooperative study in the United States and determined that higher

Table 1. TULANE DOSAGE FOR HEATED PERFUSION FOR LIMB MELANOMA*

Drug	Upper Limb		Lower Limb	
	Range (mg/kg)	Maximum (mg)	Range (mg/kg)	Maximum (mg)
Single drug				
Melphalan	0.6–1.0	65	0.8–1.2	100
TSPA	0.6–1.0	65	0.8–1.2	75
HN_2	0.3–0.6	30	0.4–0.8	40
Cisplatin	1.0–2.0	100	1.0–4.0	150
Multiple combinations				
Melphalan	0.4–0.7	45	0.5–0.8	60
TSPA	0.2–0.3	25	0.4–0.5	35
Melphalan or TSPA	0.5–0.7	45	0.5–0.9	60
Dactinomycin and HN_2	0.006–0.01	0.5	0.008–0.012	0.75
	0.07–0.11	10	0.08–0.15	12

* Fractional doses into the arterial line. Reservoir volume of 500 mL of 250 mL whole blood and 250 mL balanced electrolyte solution.
TSPA = triethylene thiophosphoramide.

doses by limb volume up to 16 mg/L can be used with the current melphalan preparation.[26] Currently, they recommend 14 mg/L of limb volume for upper limbs and 16 mg/L of limb volume for lower limbs. Limb toxicity increases with dosages over 13 mg/L of upper limb volume, and 10 mg/L of limb volume is safe for lower limbs. These dosages may be increased to 12 to 14 mg/L in good-risk patients with advanced disease.

We strongly recommend that persons interested in developing this technique visit an institution at which experience has been accumulated so that they can become familiar with indications for dosage and the variations in administration.

Patient Experience at Tulane

From 1957 to 1992, 1521 patients have been perfused on 1756 occasions at CHNO, Tulane, and most of the

Table 2. REPORTED DOSAGES FOR HYPERTHERMIC PERFUSION FOR LIMB MELANOMA

Investigator	Drug	Limb/Dosage	Route and Dosage
Fletcher[19]	CDDP	Arm, 125 mg/m^2 Leg, 250 mg/m^2	PR 1/2 dose at 5 min intervals
Pfefferkorn and Dildocher[20]	DTIC	Arm, 1 g/m^2	PR given in 3–4 divided doses every 5 min
Aigner	I-PAM	Arm, 10 mg/L	IA infusion
	CDDP	Leg 15 mg/L	PR, single dose
Ghussen *et al.*[21]*	I-PAM	Arm, 1 mg/kg (80 mg limit) Leg 1.5 mg/kg (100 mg limit)	IA 1/4 dose every 15 min
Wieberdink *et al.*[22]	I-PAM	10 mg	IA infusion
Lejeune *et al.*[25]†	Stages I and II		
	I-PAM	Arm, 20 μg/ml†	IA, single dose
	I-PAM	Leg, 40 μ/ml†	PR, single dose‡
	Stage III		
	I-PAM	Arm, 30 μg/ml†	IA, single dose
	I-PAM	Leg, 60 μg/ml†	PR, single dose‡
International Cooperative Melanoma Group	I-PAM	Arm, 13 mg Leg, 10 mg	PR, single dose‡

PR = Pump reservoir, IA = intra-arterial line. L = liter of limb volume; CDDP = cisplatin; DTIC = dacarbazine; I-PAM = melphalan.
* Perfusate volume is 1000 mL of whole blood followed by rinse of 1000 mL of whole blood.
† Based on exchangeable limb blood volume.
‡ Perfusate temperature reduced to 38°C during administration of drug and for 10 minutes thereafter.

Table 3. REGIONAL PERFUSION FOR MELANOMA BY PRIMARY SITE, SEX, AND PERFUSION AREA

Primary Site of Melanoma	Total No. of Patients	Male	Female	Regional Perfusion Area				
				Upper Limb	Lower Limb	Head and Neck	Pelvis	Breast
Head and Neck	34	22	12	1*	3*	30		
Adj. Trunk†	110	73	37	110				
Arm	173	75	98	169	4*			
Forearm	62	34	28	60	2*			
Hand	17	9	8	14	3*			
Finger (15 = Subungual)	22	10	12	22				
UPPER LIMB	384	201	183	375	9			
Skin of Breast	4	1	3					4
Pelvis	14	3	11				14	
Adj. Trunk†	19	13	6		19			
Thigh	74	21	53		74			
Leg	363	83	280	5*	355		3	
Foot	191	107	84	4*	187			
Toe (21 = subungual)	56	29	27		56			
LOWER LIMB	703	253	450	9	691		3	
GRAND TOTAL	1139	480	559	385	703	30	17	4

* Palliative perfusion of metastatic melanoma in Stage IV disease.
† Primary melanoma in skin of adjacent trunk in area included in perfusion field.

other hospitals in New Orleans. Of these, 1139 patients were diagnosed with melanomas, 184 with carcinomas, 166 with sarcomas, and 32 with glioblastomas of the brain. Of the 1139 patients with melanomas, 1347 perfusions were performed—981 were perfused on one occasion, 120 on two occasions, 28 on three occasions, 8 on four occasions, and 2 on five occasions. Perfusion by primary tumor site and perfusion area are shown in Table 3. A total of 386 upper limb perfusions through the subclavian or axillary vessels were included. Seven hundred two patients underwent lower limb perfusions through the common femoral or external iliac arteries. There were 34 patients with melanomas of the head and neck distributed over the scalp, face, oropharynx and ear, 30 of whom were perfused through the external carotid vessels and 4 of whom had limb perfusions for distant metastatic disease. Fourteen patients with penile, vulva, rectal, or anal melanomas or skin of the lower trunk received pelvic perfusions through the distal aortas. Three patients had pelvic perfusions for metastases from lower limbs. Four patients had "breast" perfusions through the proximal subclavian vessels to include the internal mammary artery distribution for lesions arising in the skin of the breast that involved the upper anterior chest, axillary nodes, or both.

The M.D. Anderson Staging System is used because it is remembered easily and is used widely for limb perfusion. Including limb and other sites, there are 471 patients with stage I (localized primary melanomas), 36 with stage II (recurrent local tumors or intransit disease within 3 cm of primary tumors), 148 with stage IIIA (intransit regional disease beyond 3 cm and positive nodes), 188 with stage IIIB (positive regional nodes) 152 with stage IIIAB (with intransit regional disease and positive nodes) and 144 with stage IV (distant metastases).

The age distribution of the entire group of patients with melanoma perfusions is shown in Figure 2. Very few prepubertal patients underwent perfusions, and none were younger than 11 years of age. Few elderly patients underwent perfusions, but one in the 90-year-old age group was treated. The majority (271) of patients 50 to 59 years of age. There were 480 men and 659 women (Table 3). Racial distribution included 1080 white patients (445 men, 635 women) and 59 black patients (35 men and 24 women). Forty-four black patients had primary tumors on the foot and toe, whereas only three had primary tumors on the hand or finger.

More than a dozen Tulane faculty surgeons were involved in this 35-year experience. Many cases were performed by residents or fellows under direct faculty supervision. The faculty surgeon was responsible for the final selection of the dose, timing of the perfusion and excision procedures, decision to include lymph node dissection, width of excisions for the primary lesion, and other technical decisions. Six hundred cases were done by the senior author; Creech performed 183 before his untimely

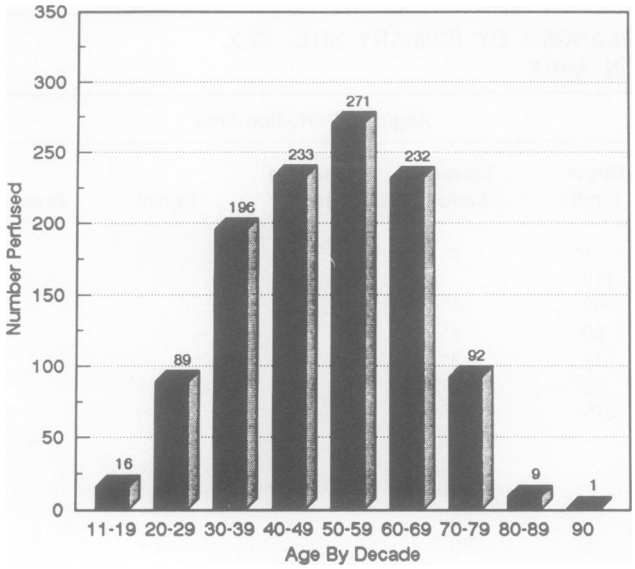


Figure 2. Distribution by age of melanoma perfusion patients.

death in 1967; other faculty surgeons performed 536 perfusions.

RESULTS

Limb Primaries

Early in this project, it was noted that the difference between survival and disease-free survival in melanoma patients was small, i.e., <5% at 10 years. Consequently, we report our results in survival because this represents an easily obtainable definitive end point. Survivals also are presented in cumulative life-table methods as described by Cutler and Ederer.[27] When the project began, melanomas were classified pathologically as *in situ* or invasive. In 1969, the Clark's level of invasion[28] and in 1970, Breslow's thickness in millimeters[29] were added as reliable prognostic indicators; classification of melanomas by the various histologic subtypes also was added. It has not been possible to obtain sections of the primary tumors in all referred cases. For many patients with metastatic disease, only slides of the metastases were available. In reviewing available sections, six patients with localized primary limb melanoma were later classified as Clark's level II. None of these patients died of disease, although one had a local recurrence, requiring further treatment. Four hundred fifty-eight patients had stage I limb primary tumors of levels III to V. During this 35-year period, the percentage of patients unable to be observed for follow-up was approximately 5%.

The survival times for all patients are shown, by stage of disease, in Figure 3. Cumulative survival to 20 years is shown; however, confidence levels for survival at 15 and 20 years are decreased because of loss to follow-up. It must be emphasized that although all patients had chemotherapy perfusion, the majority of the patients also had excisional surgery.

In stage I, only one patient, a 68-year-old black woman, refused surgical excision of a large acral lentiginous melanoma of the palmar surface on the hand; however, she had a complete response to perfusion, dying of cardiovascular disease 15 years later. The rest of the patients with primary lesions had wide local excisions, decreasing in width through the years, and many have had regional lymph node dissections (RLNDs). The patients in stage II were treated by perfusions, excisions, and RLNDs, where indicated.

In stage IIIA, patients with intransit metastases generally had excisions of the satellites or subcutaneous intransit disease if the metastases were few, usually less than five. In stage IIIB, all patients had lymph node dissections, although our node dissections were more conservative for patients who had perfusions than for those who did not. Thin flaps and extensive clean dissections of subcutaneous tissue, combined with high-does regional chemotherapy, led to increased wound complications. Patients with stage IIIAB disease usually have

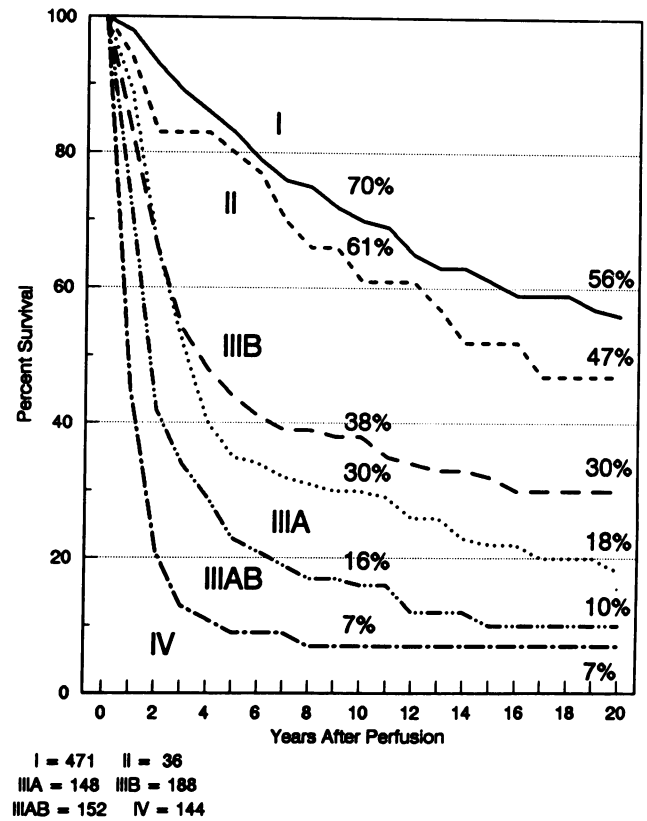


Figure 3. Regional chemotherapy for melanoma—cumulative survival by stage for 1139 patients.

Table 4. REGIONAL PERFUSION FOR 1088 LIMB MELANOMA PATIENTS SURVIVAL BY STAGE

Stage	No. of Patients	Cumulative Survival Percent			
		5 yr	10 yr	15 yr	20 yr
I. Primary	458	83	70	61	56
Male	159	73	57	47	43
Upper	75	86	71	59	56
Lower	84	62	45	37	32
Female	299	89	77	70	63
Upper	105	88	78	73	66
Lower	194	89	77	69	62
All with RLND	310	87	74	66	63
All without RLND	148	76	61	52	42
II. Local recurrence	36	80	61	52	47
Male	12	83	31	17	17
Female	24	78	78	69	61
III. Regional metastases	468	36	29	23	21
(A)Intransit	143	36	30	22	18
(B)Nodes	180	45	39	32	30
(AB)Intransit and Nodes	145	23	17	10	10
IV. Distant metastases	126	10	8	8	8
Total	1088				

RLND = regional lymph node dissection.

RLNDs and excisions of intransit metastases, if few in number.

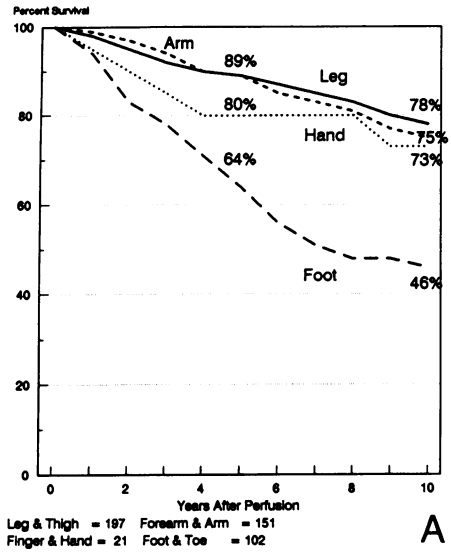
Patients with stage IV disease usually had additional therapy to regional perfusions, such as excisions of recurrences, where possible; node dissections—if feasible, occasionally, regional intra-arterial infusions; systemic chemotherapy; and, rarely, irradiation or immunotherapy. Patients with stage IV disease included 45 patients with positive iliac or supraclavicular nodes that were removed by node dissection. Although this was a poor-prognosis group, these patients should be downstaged because at 5 and 10 years, they have a consistent 14% survival. Two patients who subsequently developed positive iliac nodes have had sequential recurrences in nodes in the opposite groin and survive at 8 and 17 years. Both patients were treated by perfusions and RLNDs of ipsilateral and contralateral external iliac nodes, but at different times. In all stages of limb melanoma, a survival differential exists between men and women, with women favoring the latter (Table 4). In stage 1, the survival of men at 10 years was 57%, compared with women at 77%. In stage II, 10-year female survival was higher, 78% to 31%. In advanced stages, the differential was less, varying from 7% in stage IV to 14% in Stage IIIAB.

Survival by site has been presented by stage I and II, in which survival by leg and arm are almost identical up to 10 years, survival for leg primary at 5 and 10 years is 89% and 78%, respectively, and for arm survival at 10 years is 89% and 75%, respectively. Survival by stage III again shows similar results for leg and arm, but hand and foot have a marked decrease in survival. (Figs. 4A and 4B)

Survival by histology confirms expected behavior according to pathologic type. Figure 5 shows survival for 434 patients, classified by histopathologic type, for all stages treated by perfusion and surgical excision, when feasible.

Survival by perfusion drug is shown in Figure 6. Melphalan was the drug of choice, as indicated by the 753 patients treated with this agent. The use of melphalan and TSPA was smaller, with 161 patients; even fewer patients were treated with the combination of TSPA, dactinomycin, and HN_2—112 patients. Thirty-one patients were treated with HN_2 alone. At 10 years, a fairly marked difference occurred in the survival of all patients, with the best survival in group treated with the combination of TSPA, dactinomycin, and HN_2. One observation as to the increase in survival with the triple drug combination is that it was used more frequently from the late 1970s and 1980s, when survival times for all patients were improving, compared with results from the 1960s.

Survival in patients with stage I perfusions with and without regional node dissections produced a number of interesting observations (Figs. 7A and 7B). As mentioned previously, node dissection was determined by the surgeon responsible for the patient. Generally, the patients with poorer prognoses received node dissections



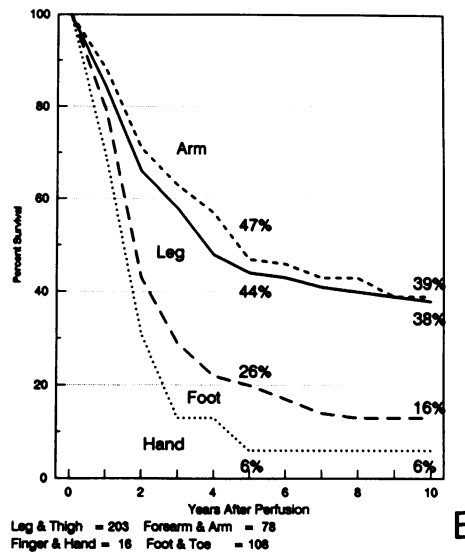


Figure 4. (A) Regional chemotherapy for melanoma—survival for stages I and II patients by primary site. (B) Regional chemotherapy for melanoma—survival for stage III patients by primary site.

and the patients with better prognoses did not. If a suspicious node was seen during exposure of the blood vessels, a biopsy was obtained. If the biopsy was positive, RLND usually followed. For all stage I patients, the upper limbs did better than lower limbs, and those with node dissections did better than those without. In women, the survival differences were small, but in men, the differences were much more obvious. Thus, for men with lower limb melanomas, RLND usually is included.

Survival for 2, 5, and 10 years for patients with stage I limb melanomas, according to growth characteristics, thickness, and level, is shown in Table 5. As noted pre-

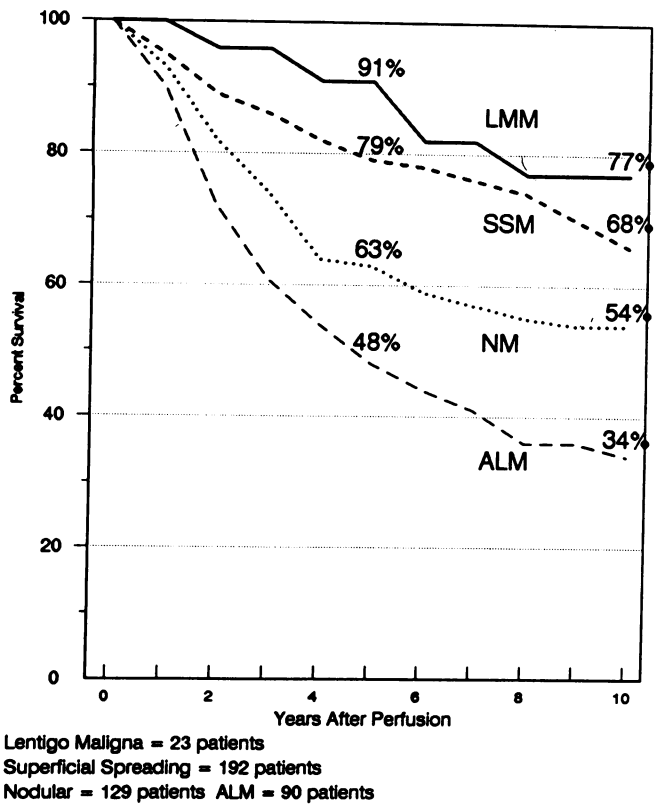


Figure 5. Regional chemotherapy for melanoma—survival by histology of 434 patients, including all stages.

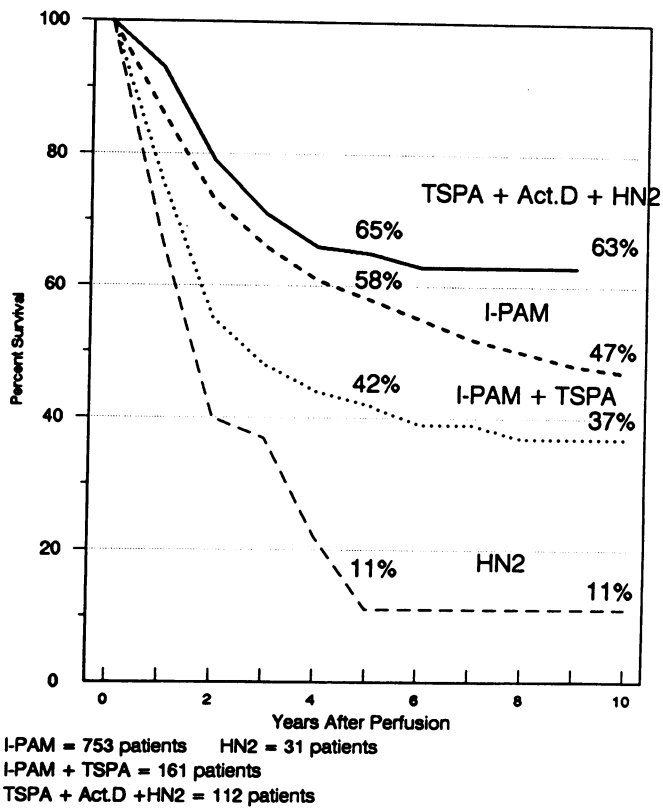


Figure 6. Regional chemotherapy for melanoma—survival by drug of 1057 patients, including all stages.

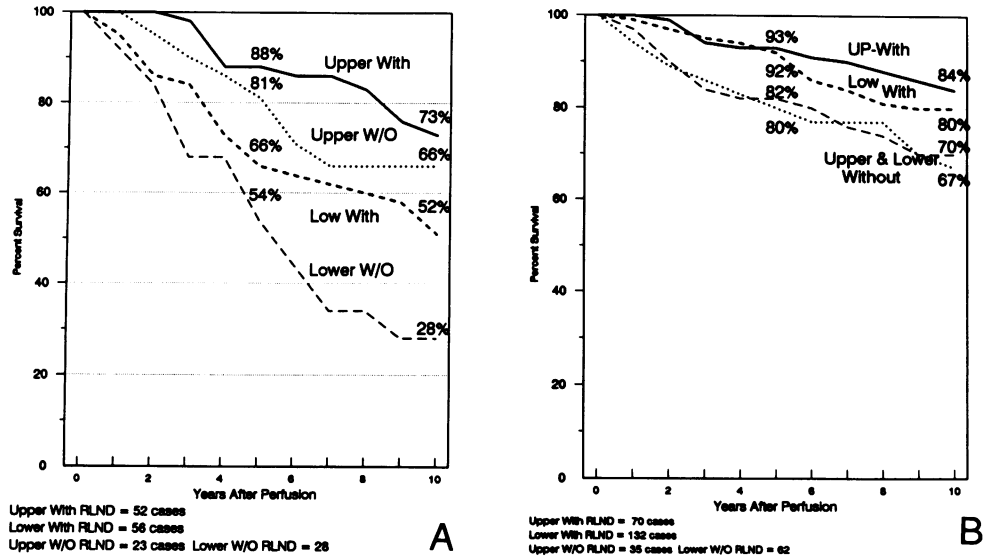


Figure 7. Regional chemotherapy for melanoma—survival for stage I patients with or without regional lymph node dissection by sex. (A) Female patients; (B) male patients.

viously, a few patients who underwent treatment early in the program, before the introduction of levels and thicknesses on subsequent slide review, were found to have thicknesses less than 0.75 mm, or were level II. Currently, we only include patients with level III (1.5 mm or thicker) for perfusion. Survival in patients with <0.75-mm thicknesses show slight loss at 5 and 10 years; although lentigo maligna melanomas seldom produce fatality, there was reduction in survival at 10 years to 82%. In nodular melanoma or acral lentiginous melanoma, survival is better than expected. Also, level V and (deep) melanoma 5 mm and deeper reveal long-term survival in this group of cases that is not considered curative by some authorities.

Table 5. SURVIVAL RATES IN STAGE I PATIENTS WITH MELANOMA OF THE LIMB BY GROWTH TYPE, THICKNESS, AND LEVELS WHERE OBTAINABLE 1957–1992

Characteristic	Patients	Cumulative Survival		
		2 yrs	5 yrs	10 yrs
Growth type				
Superficial spreading	132	98	91	78
Lentigo meligna	18	100	94	82
Nodular	71	94	84	74
Acral lentiginous	56	84	62	44
Thickness (mm)				
<0.75	18	94	94	89
≥7.5–<1.50	64	100	90	83
≥1.50–<3.00	102	95	87	73
≥3.00–<5.00	35	88	59	50
≥5.00	17	80	67	29
Clark level				
II	6	100	100	100
III	148	98	91	76
IV	220	93	85	73
V	33	78	58	39

Non-Limb Primaries

Survival of patients with non-limb primary tumors, including 34 of the head and neck, 4 of the skin of breast, and 17 of the pelvis, was much poorer than survival of patients with limb primary tumors. No perfusions for the former two sites have been done since 1971; however, pelvic perfusions for melanoma occasionally are performed in selected situations. Four patients had breast perfusions for melanoma developing in the skin of the upper anterior chest; although it was thought that these patients might benefit from this, they died of their disease in less than 2 years.

Ten patients with melanomas of the head and neck were classified as stages I and II. Seventeen patients were classified as stage III, and seven were classified as stage IV. Four of the latter seven patients had melanoma of the head and neck sites with metastases to limbs. The survival time for these four patients was less than 1 year. Five of the ten patients classified at stages I and II had long disease-free survival times of 12 to 30 years; they included ear, scalp, cheek, and orbital primary tumors. All had additional excisional surgery, including three neck dissections; two had orbital exenterations. The five remaining stage I cases died within 2 years. It would seem that five long-term survivors warrant further evaluation, and it may be that perfusion was of greater benefit than previously thought. Of the 17 stage III cases, two patients lived more than 5 years, nine died after less than 2 years,

Table 6. MULTIPLE PERFUSIONS 158 MELANOMA PATIENTS BY STAGE AND PERFUSIONS

Stage	Patients	No. of Perfusions 2	3	4	5	Perfusions
I	31	22	6	3	0	74
II	8	7	1	0	0	17
IIIA	50	32	12	5	1	125
IIIB	14	11	3	0	0	31
IIIAB	34	30	4	0	0	72
IV	21	18	2	0	1	47
	158					
Perfusions		240	84	32	10	366

Table 7. CUMULATIVE SURVIVAL OF MELANOMA BY STAGE 139 PERFUSION PATIENTS *VS.* 158 PATIENTS WITH MULTIPLE PERFUSION 1957–1992

Stage	Survival (%) 5 Yr All *VS.* Multiple		10 Yr All *VS.* Multiple	
I	83	68	70	35
II	80	—	61	—
III				
A	35	25	30	16
B	45	32	38	10
AB	23	29	16	11
IV	9	14	7	0

and six survived 2 to 5 years. The remaining patients classified as stage IV cases died of disease within 1 to 1½ years. The 17 patients with pelvic perfusions for melanomas were all considered poor prognosis cases. There were 3 patients with stage I disease, 3 with stage IIIB disease, and 11 with stage IV disease. The patients with stage I disease survived as follows: one less than 2 years; one died—status unknown at 5 years, and one with vulva melanoma survives disease-free at 18 years. The 11 patients with stage IV disease all were dead or unable to be observed for follow-up by 2 years.

MULTIPLE PERFUSIONS FOR RECURRENT MELANOMA

The problem of managing regional recurrent melanoma after previous treatment has been challenging. The behavior of melanoma encompasses a wide range from chronic indolent disease to the rapidly lethal variant. Fortunately, a considerable number of patients will have regionally confined disease responsive to treatment for long periods. Included in this group are the 158 patients treated by multiple perfusions.[31] Our data include 155 patients with limb melanomas and 3 with head and neck melanomas receiving 366 perfusion (Table 6).

The cumulative survival for the multiple perfusion series compared with the entire series at 5 and 10 years is shown in Table 7. The survival for multiple perfusion from time of first perfusion is less in all categories compared with the entire series, but many remarkable complete responses occurred after the second or additional perfusions. One occurred after the fourth perfusion in a 36-year-old man. This patient had short temporary responses after the first three perfusions, but converted to complete response after the fourth perfusion with HN_2. Alive at last follow-up at 66 years of age, he remains disease-free after 28 years since his last perfusion; however, he lost the treated limb because of arterial disease 16 years after the original perfusion. Repeat perfusions are indicated on one or two occasions for good-risk patients with regional recurrent tumors if another drug or combination of drugs seems promising; for technical reasons, such as hyperthermic perfusion, if failure follows normothermic or heated perfusions (hyperthermia was not used widely until the 1970s); or for recurrence in more proximal areas, such as the development of positive groin nodes after a common femoral perfusion for lower-limb disease.

Figure 8 shows the results in stage I disease for multiple perfusions. Eight patients are alive and disease-free 5 to 33 years after a second perfusion or additional perfusions; six had three perfusions, and four had three perfusions. One is alive with disease at 8 years, and one died, disease-free 16 years after a second perfusion at 3 years. Remarkably, 11 of 21 patients dying with melanomas died 5 or more years after two or more perfusions. One of these patients had no apparent melanoma for 23 years, but developed a recurrence in the proximal limb that failed to respond to a second perfusion, dying within 6 months after the second procedure. Two deaths in this group resulted from chemotherapy complications, and one postoperative death was a result of myocardial infarct. No limb loss from chemotherapy was experienced.

COMPLICATIONS

Complications were common during the developmental years of this procedure. Combining cancer and vascular surgery with regional chemotherapy in patients often with advanced neoplastic disease and in poor condition increased morbidity and mortality. The addition of hyperthermia in 1968 resulted in added further vascular and limb complications, until the chemotherapy doses

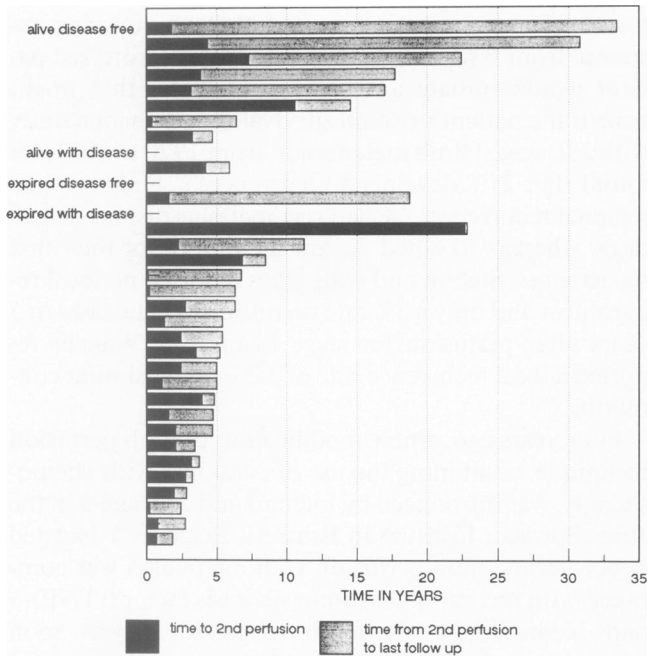


Figure 8. Survival in years of 31 stage I patients receiving multiple perfusions for recurrent melanoma. Patients alive, melanoma free (8), alive with melanoma (1), dead, melanoma free (1), dead with melanoma (21).

were reduced. Although hyperthermia and perfusion resulted in an increase in regional complication, the lowered doses resulted in fewer systemic complications from bone marrow depression.

Wound, limb, and systemic complications through 1982 have been documented in recent articles[10,31]; however, in the last 10 years, complications have not been a serious problem. One patient with hypersensitivity to nitrogen mustard has had severe neuritis and limitation of limb function after perfusion.

The most serious complications confined to the developmental period were mortality resulting from leukopenia and thrombocytopenia after poor isolation, high dosage, or patient hypersensitivity to a particular drug. From 1957 to 1966, 42 patients were reported with white blood cell counts below 2000, and 21 patients were reported with counts below 1000, resulting in six chemotherapeutic deaths. The development of white cell and platelet transfusion, and more recently, granulocyte-stimulating factor, have eliminated deaths from bone marrow depression.

Three operative deaths occurred before 1964 due to cardiopulmonary problems that possibly could have been avoided by better case selection. One operative death occurred in 1989, in an elderly woman; during the post-perfusion period, she developed ileus and ischemic bowel complications from adhesions that had developed at previous bowel surgery.

Amputations as a result of complications after perfusion have been uncommon, but have occurred in eight patients, all before 1966. Four patients required amputations because of arterial thromboses, two patients required amputations as a result of massive venous thromboses, and two patients required amputations as a result of nerve or muscle damage. In some centers, where hyperthermia and high dosages of drugs are used, prophylactic fasciotomies are performed to prevent compartment syndrome. Recently, it was concluded that the additional procedure did not increase morbidity associated with limb perfusion.[32] In recent years, two patients required amputations followed by perfusion for known peripheral vascular disease, in attempts to save limbs with intransit metastases.

Temporary loss of nails or sloughing of superficial skin of the palms and soles are seen occasionally. Most patients experience cessation of hair growth in the perfused limb for several months, and some experience transit neuralgia; however, currently, long-term disability is seldom seen. Tumor response and regional toxicity tend to be unpredictable. A number of our patients with long-term complete responses have not received high chemotherapy doses. Others with high regional doses, as judged by regional toxicity, may have little tumor response.

DISCUSSION

In the late 1950s, when perfusion therapy was instituted, surgical treatment of melanoma was not very effective. Many patients presented with advanced or neglected disease. Excisional surgery was the only reliable therapeutic modality, and in attempts to control this serious and often fatal neoplasm, surgical approaches had become more and more radical. Recommendations for standard excision for primary disease included 4 cm or greater margins of skin, excision of underlying muscle fascia, and major amputations for recurrent or intransit limb metastases, including forequarter or hindquarter amputations. Chemotherapy was considered ineffective, with temporary response rates of 10% or less. Irradiation was palliative at best.

In 1962, Ackerman and Del Regato reported expectation of 5-year surgical cure rates for stage I melanoma to be 45%.[33] Patients with microscopically positive lymph nodes after node dissections could expect a 15% 5-year control rate and a 10% salvage rate with clinically positive nodes. The complete and persistent response in the first patient treated by perfusion for satellitosis was considered miraculous. The responses obtained in patients with advanced disease led us to believe adjunctive therapy in poor-risk stage I disease was appropriate, but by 1962, we had treated only six melanoma patients by perfusion as an adjunct to surgery.[34]

As of 1972, 160 patients with limb melanomas had adjunctive perfusions in addition to surgical therapy; 27 patients received wide excisions only, and 133 had wide excisions plus RLNDs.[34] Nineteen of 24 patients in the group that underwent wide excisions and 12 of 13 in the group that had lymph node dissections were disease-free. These survival rates were better than concurrent reports obtained with surgery only. Other centers using perfusion techniques had similar results. At that time, we did not feel the need for a prospective, randomized study.

In 1984, Ghussen and associates reported results with melphalan by perfusion as an adjunct to surgical therapy.[21] This study was closed after 3 years because only five recurrences were reported in the perfusion group, compared with 25 in the surgical-only group. In 1988, these same patients were re-evaluated, and six relapses had occurred in the 53 patients in the group that underwent perfusions compared with 26 of 54 in the control group. Three patients in the perfusion group and 11 in the control group had since died of their disease.[35]

In 1984, the World Health Organization Melanoma Study Group, the Perfusion Committee of the European Organization for Research and Treatment of Cancer, and the North American Perfusion Group, with the help of the Southwest Oncology Group, organized a prospective, randomized study for the adjunctive use of perfusion with melphalan plus excision in comparison with a surgical-only group.

As of December 1992, a preliminary report was presented at the International Columbus meeting on Surgical Oncology in Genoa, Italy. Lejeune and colleagues reported 785 patients who had been so treated[36]; these were stage I patients with melanomas 1.5 mm or thicker. The treatment arm included wide local excision of the primary tumor and isolated perfusion, whereas the control arm included wide excision only. The decision whether to perform elective node dissection was left to the institutional policy. Rates of lymph node metastases, intransit metastases, and local recurrences were 13.5%, 1.5%, and 2%, respectively, in the perfusion arm *versus* 21.9%, 6%, and 3.3%, respectively, in the control arm. Eight percent developed distant metastases as the first sign of progression in the perfusion arm compared with 6% in the control arm. The preliminary results showed that perfusion may reduce regional node metastases and a decrease was seen in intransit metastases and local recurrence. Thus far, survival times appear to be the same for both groups, but the study will be closed in April 1994 and final reports will appear thereafter.

One way of evaluating the effects of chemotherapeutic limb perfusion is to determine the incidence of local or regional recurrence in the perfused patient. Presumably, the patient who developed distant recurrence without regional recurrence had the metastases at the time of perfusion. The anticipation existed that an immune response from lysis of tumor in the noncompromised patient would initiate an immune response that might benefit the patient's overall survival. In a previous study with 336 stage I limb melanomas, from 1970 to 1981, we found that 21% developed recurrences.[37] Only 9% had regional recurrence, 2% had regional plus distant metastases, whereas 10% had distant metastases for their first recurrences. Stehlin and colleagues reported no local recurrences and only a 3% rate on intransit metastases in 5 years after perfusion for stage I lesions.[38] Wagner reported a local recurrence rate of 3.2% under similar conditions.[39]

Four years ago, a new modification of limb perfusion technique, combining the use of cytokines with chemotherapy, was introduced by Lienard and colleagues at the Jules Bordeau Institute in Brussels, Belgium.[40] Isolated hyperthermic limb perfusion with melphalan was combined with recombinant tumor necrosis factor (rTNF)-α and recombinant interferon (rIFN)-α. It was soon learned that fluid loading and dopamine infusion of 3 μg/kg/min, starting before administration of rTNF-α and continuing for 48 hours after the perfusion, was required to prevent morbidity and mortality from capillary leak syndrome. Complete response occurred in 26 of 29 patients, with partial response in the remaining 3. Mean duration of response was 33+ weeks, ranging from 8 to 112 weeks, as reported in 1991.

The perfusion program introduced in 1957 has continued to attract interest and expand. More than 34 presentations were made concerning regional chemotherapy at the III International Congress on Melanoma in Venice in March 1993. Twelve presentations and abstracts are listed in the current SSO program in March 1993. Although there seems to be increasing interest in Europe and Australia in these procedures, a number of centers in the United States continue to produce excellent studies in this field.

CONCLUSION

Safe techniques for regional chemotherapy by perfusion are now available for most anatomical body areas and organs.

The method is particularly effective for obtaining regionally confined high dosage of toxic chemotherapeutic agents that cannot be tolerated by systemic administration.

The best responses have been obtained in limb melanoma, particularly with recurrent or intransit disease and lymph node metastases.

Adjunctive chemotherapy by perfusion to surgical excision reduces local recurrences, regional metastases, and lymph node involvement.

Regional chemotherapy has contributed to the reduction of major amputations for the control of limb melanoma. Currently, major amputation rarely is required.

Multiple regional chemotherapeutic perfusions can produce long-term useful survival in the patient with indolent chronic recurring melanoma.

Acknowledgments

The authors thank Gae O. Decker for her assistance in editing the manuscript; Cynthia Keppley, Ph.D., Marilyn Campbell B.S., R.N., and Kennon Rohbock, B.A., for data analysis; Helen M. Ritter for preparation of the manuscript; and the faculty members, residents, fellows, data collectors, research technicians, and cardiovascular pump technicians of the Tulane University School of Medicine, Department of Surgery, who participated in this program. The authors also thank the nurses and operating room personnel in many hospitals in the New Orleans area who helped care for their patients.

References

1. Ryan RF, Krementz ET, Creech O, et al. Selected perfusion of isolated viscera with chemotherapeutic agents using extracorporeal circuit. Surg Forum 1957; 8:158–161.
2. Luce JK. Chemotherapy of malignant melanoma. Semin Oncol 1975; 2:179.
3. Creech O Jr, Krementz ET, Ryan RF, Winblad JW. Chemotherapy of cancer: regional perfusion utilizing an extracorporeal circuit. Ann Surg 1958; 148:616–632.
4. Krementz ET, Creech O Jr, Ryan RF, Reemstma K. An appraisal of cancer chemotherapy by regional perfusion. Ann Surg 1962; 156:417.
5. Krementz ET, Knudson L. The effect of increased oxygen tension on the tumoricidal effect of nitrogen mustard. Surgery 1961; 50: 266–271.
6. Cavaliere R, Ciocatto EC, Giovanella BC, et al. Selective heat sensitivity of cancer cells: biochemical and clinical studies. Cancer 1967; 20:1351–1381.
7. Stehlin JS Jr, Giovanella BC, Ipolyi PD, et al. Result of hyperthermic perfusion for melanoma of the extremities. Surg Gynecol Obstet 1975; 140:339–348.
8. Miller RC, Ketcham AS. The effect of heparin and warfarin on primary and metastatic tumors. J Med 1974; 5:23–31.
9. Krementz ET, Ryan RF, Muchmore JH, et al. Hyperthermic regional perfusion for melanoma of the limbs. *In* Cutaneous Melanoma. 2nd Edition. Philadelphia, PA: JB Lippincott Co, 1992, pp 403–426.
10. Krementz ET. Regional perfusion: current sophistication, what next? Cancer 1986; 57:416–432.
11. Aust JB, Griffen WD, Ausman RK. Isolated perfusion of head and neck tumors. Presented at the Annual Meeting of the Society of Head and Neck Surgeons; 1959; Washington, DC.
12. Ausman RD, Aust JB. Isolated perfusion of the liver with HN2. Surg Forum 1960; 10:77–79.
13. Mulcare RJ, Solis A, Fortner JG. Isolation and perfusion for cancer chemotherapy. J Surg Res 1973; 15:87–95.
14. Aigner K, Walther H, Tonn J, et al. First experimental and clinical results of isolated liver perfusion with cytotoxics in metastases from colorectal primary. Rec Res Cancer Res. 1983; 86:99–102.
15. Woodhall B, Hall K, Mahaley S, Jackson J. Chemotherapy of brain cancer: experimental and clinical studies in localized hypothermic cerebral perfusion. Ann Surg 1959; 150:640–652.
16. Dedrick RL, Oldfield EH, Collins JM. Arterial drug infusion with extracorporeal removal. I. theoretical basis with particular reference to the brain. Cancer Treat Rep 1984; 68:373–380.
17. Aigner KR. Drug filtration in high-dose regional chemotherapy. *In* Aigner KR, Patt YZ, eds. Advances in Regional Cancer Treatment: Contributions to Oncology. Basel: Karger, 1988, p 261.
18. Luck JM. Action of p[DI(2-cloroethyl)]-amino-L-phenylalanine on Harding-Passey mouse melanoma. Science 1956; 123:983–984.
19. Pfefferkorn RO, Dildocher MS. Regional perfusion for melanoma of the extremities. J Extracorporeal Technol 1982; 14L:475–479.
20. Fletcher WS, Pommier RF, Woltering EA, et al. Pharmacokinetics and results of dose escalation in cisplatin hyperthermic isolation limb perfusion. Ann Surg Oncol 1994; (in Press).
21. Ghussen F, Nagel K, Groth W, Muller JH, Stutzer H. A prospective randomized study of regional extremity perfusion in patients with malignant melanoma. Ann Surg 1984; 200:764–768.
22. Wieberdink J, Benkuizen C, Braat RP, et al. Dosimetry in isolated perfusion of the limbs assessment of perfused tissue volume and grading of toxic reactions. Eur J Cancer Clin Oncol 1982; 18:905–950.
23. Mendoza E, Krementz ET, Murayama N. Comparison of optimal melphalan dosage and toxic reactions for regional perfusion by perfused tissue volume and body weight. Proc ASCO 1985; 4 (abstract).
24. Krementz ET, Saha S. Limb perfusion with melphalan for melanoma by increased dose and dilution compared to the standard technique: a pilot study. Reg Cancer Treat 1989; 2:233–237.
25. Lejeune FJ, Ghanem G, Lienard D, Ewalenko P. Assessment of hematocrit method for dosimetry of cytostatics in isolation perfusion. Reg Cancer Treat 1989; 2:82–86.
26. Boddie AW, Briele H, Krementz E, et al. A phase I study of melphalan in 40°C isolated limb perfusion using packed red blood cells and lactated ringers perfusate. Proc ASCO 1992; 11:A1208 (abstract).
27. Cutler SJ, Ederer F. Maximum utilization of the life table method in analyzing survival. J Chron Dis 1958; 86:699–712.
28. Clark WH Jr, From L, Bernadino EA, Mihm MC Jr. The histogenesis and biologic behavior of primary human malignant melanomas of the skin. Cancer Res 1969; 29:705–715.
29. Breslow A. Thickness, cross-sectional areas and depth of invasion in the prognosis of cutaneous melanoma. Ann Surg 1970; 172: 902–908.
30. Krementz ET, Muchmore JH, Sutherland CM. Intra-arterial infusion chemotherapy for melanoma. Melanoma Res 1994; (in press).
31. Krementz ET, Carter RD, Sutherland CM, Muchmore JH. Chemotherapy by regional perfusion for limb melanoma. Am Surg 1987; 53:133–140.
32. Olieman A, Schraffordt-Koops H, Geertzen J, et al. Functional morbidity of hyperthermic isolated perfusion of the extremities. Presented at the Society of Surgical Oncology 47th Annual Cancer Symposium; March 17–20, 1994; Houston, Texas (abstract).
33. Ackerman LV, DelRegato JA. Cancer: Diagnosis, Treatment and Prognosis. St Louis: CV Mosby, 1962, p 224.
34. Krementz ET, Ryan RF. Chemotherapy of melanoma of the extremities by perfusion: Fourteen years clinical experience. Ann Surg 1972; 175:900–917.
35. Ghussen F, Kruger I, Smalley RV, Groth W. Hyperthermic perfusion with chemotherapy and melanoma of the extremities. World J Surg 1989; 13:598–602.
36. Lejeune FJ, Vaglini M, Schraffordt-Koops H, et al. A randomized trial on prophylactic isolation perfusion for stage I high risk (i.e. >1.5 mm thickness) malignant melanoma of the limbs. An interim report. Presented at the Special International Columbus Meeting on Surgical Oncology; December 3–5, 1992; Genoa, Italy.

37. Krementz ET, Ryan RF, Muchmore JH, et al. Hyperthermic regional perfusion for melanoma of the limbs. Cutaneous Melanoma. 2nd ed. Philadelphia, PA: JB Lippincott Co, 1992, pp 403–426.
38. Stehlin JS, Greeff PJ, de Ipolyi PD. Heat as an adjuvant in the treatment of advanced melanoma. An immune stimulant? Houston Med J 1988; 4:61–82.
39. Wagner DE. A retrospective study of regional perfusion for melanoma. Arch Surg 1976; 111:410–413.
40. Lienard D, Lejeune FH, Ewalenko P. Intransit metastases of malignant melanoma treated by high dose rTNFα in combination with interferon-Γ and melphalan in isolation perfusion. World J Surg 1992; 16:234–240.

Discussion

DR. WILLIAM S. FLETCHER (Portland, Oregon): I would like to congratulate Dr. Sutherland, Dr. Krementz and their co-authors on this landmark report of their innovative technique and their persistent effort to improve the survival of extremity melanoma.

At the time this study started, the published survival of Stage 1 node-negative extremity melanoma was 15% and the survival of Stage 2 (positive node or in-transit metastases) was 5%. Because of that dreadful experience, I went to Tulane in 1960 and learned how to do perfusions from Dr. Krementz, Dr. Ryan and Dr. Stehl. I have done perfusions ever since.

We have done 572 perfusions up to the present time. The results are exactly like everybody else's published results with this technique and with the available agents during that period of time. Survival is over 70% at 5 years for Stage 1 melanoma and essentially 53% for Stage 3. Using the M. D. Anderson classification, 3-A is with in-transit metastases, 3-B is with positive nodes, and 3-AB is both. We have not amputated an extremity for melanoma since 1965.

The concept of confining the therapy to the extremity is brilliant and it works. However, we have not really improved on the results with the original drug L-PAM. In Europe and selected centers in this country, people have been using TNF and L-PAM together with nearly 100% response rates, but the responses appear not to be durable and the perfusion results in major toxicity not confined to the limb.

The respective role of the various components of the perfusion—i.e., the drug, the heat, and the heparin—are not clear. Clinically, responses suggest a delayed cutaneous hyper-sensitivity reaction. Very recently other investigators have reported that perfusion by and in itself releases cytokines into the extremity, and I hope that someone will discuss that. Recently we have employed intralesional BCG and perfusion with L-PAM, Actinomycin D, and cisplatin with initial very good results.

In summary, while the indications and agents used continue to evolve, perfusion remains the only effective treatment for otherwise untreatable extremity melanoma. I would like to ask Dr. Sutherland and his associates what direction they plan to follow now.

DR. HIRAM C. POLK, JR. (Louisville, Kentucky): I have no questions, but I did want to rise to speak strongly in support of the thesis that Dr. Sutherland, Dr. Ryan, and Dr. Krementz have presented to you this morning.

There is the continuing lament over the lack of a prospective randomized trial out of the Tulane data. As a matter of fact, there are a number of reasons why they have not done that. The sheer weight of numbers becomes increasingly meaningful with the development of what is now 20 years actual follow-up, not actuarial follow-up. In fact, a half dozen fairly well controlled trials are now published that clearly show measurable benefit, to one degree or another, to patients who are treated by perfusion. I am persuaded by them and I wanted to comment briefly.

First of all, perfusion is the primary treatment of choice for patients with melanomas greater than 2 mm thick confined to the extremity. I think it is unequivocally the treatment of choice for patients who present with recurrent disease, still confined to a body part.

The overall salvage rates shown here are the best in the world by far. In almost every set of circumstances when perfusion has been tested by prospective trials, the tendency is either statistically significant or just numerically positive in favor of perfusion. Whether you do or do not perform elective lymph node dissection is another issue altogether.

We were able to present to the Society of Surgical Oncology at its meeting 3 weeks ago a sequence of patients that we had studied and had a remarkable elaboration of cytokines in the perfused circuit during the operation.

Now, many of you know Lienard and Lejeune have talked about carrying out perfusions with gamma interferon priming and then using TNF plus additional chemotherapy as part of their therapy. I think the results they have achieved in some desperate cases have been very good. Our own data with the spontaneous elaboration of cytokines have indicated it might be dangerous to add more to the circuit that is producing endogenous elaboration of cytokines at a high level.

Furthermore, to add to the quality of the data presented on complications of perfusion this morning, I think it is really important to address an adjunctive form of therapy and ask exactly what is its price. We have done more than 400 of these and had one death, one arm amputation, and one leg amputation.

Less than 1% major morbidity or mortality from this treatment does make it a useful adjunctive treatment. I think that this may represent the time in which more people will cautiously embrace what is a very efficacious and safe treatment.

DR. HAROLD J. WANEBO (Providence, Rhode Island): I would like to compliment the authors on the follow-up of a pioneering work started 37 years ago. It is amazing that we have heard the pioneers who began this work and who have presented an update on that data with an amazingly low complication rate and outstanding results, especially when we see 10-year survivals of 30–38% in patients with in-transit metastases, and even nodal metastases.

From my own review of the literature, it appears that patients with thick melanomas greater than 4 mm, Level 5, or acral lentiginous melanomas, seem to benefit from perfusion, even though to my knowledge the randomized data is still not in to support that.

Perfusion seems to be associated with about a 10 or maybe 15% betterment of distant disease-free survival, which is interesting, and I would ask the authors to comment on that. That is,